REMARKS

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 12, 13, 20, and 30-39 are pending in the application, with 12, 13, and 20 being the independent claims. Claims 1-11, 14-19, and 21-29 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above Amendment and the following Remarks, Applicant(s) respectfully request(s) that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

In the Office Action, at page 4, Claims 12-13 and 20 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. In particular, Claims 12-13 allegedly lacked antecedent basis and Claims 12-13 and 20 were missing "and" between step (b) and last step (c). Applicants respectfully request reconsideration of these rejections.

Applicants have amended claims 12-13 and 20 to clarify the claims and to address the concerns in the Office Action. Specifically, Applicants' have addressed the antecedent basis issue for Claims 12 and 13 and have added "and" between step (b) and last step (c) for Claims 12-13 and 20. The claims as amended particularly point out and distinctly claim the subject matter, which the applicants regard as the invention.

Applicants and the undersigned have carefully reviewed the Office Action, the remarks therein concerning clarity of the claims, and all the pending claims. By way of the foregoing amendments, Applicants have attempted to specifically address each of the comments in the Office Action concerning the clarity of the claims, and respectfully submit that the pending claims fully comply with 35 U.S.C. § 112, second paragraph. Applicants therefore respectfully requests withdrawal of the rejections of the claims.

Rejections under 35 U.S.C. § 103

In the Office Action, at page 5, Claims 12-13 and 20 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stark, et al. in view of Beach, et al. Applicants respectfully request reconsideration of these rejections.

The Examiner alleges that Stark, et al. teach cell lines transfected with vectors which express a reporter compound under the control of a regulatory region inducible directly or indirectly by a stimulating substance (e.g., interferon alpha). The reporter compound may comprise a cytotoxic compound (e.g., HPGRT), expression of which is indicated by the death of cells. The Examiner also alleges that Stark, et al. disclose a method of using the cell lines transfected with vectors, comprising the steps of exposing the cells to a test compound, stimulating the reporter gene, and assaying for activity of the reporter gene (i.e., detecting expression of reporter gene or cell death). The Examiner further alleges Stark, et al. disclose the introduction of genes into test cells to assay the introduced gene for inhibitory effects. The Examiner alleges that although Stark, et al. do not specifically teach introducing a gene library into the assay system as the test compounds and isolating the gene identified by the screening method, Beach, et al. teach retroviral vectors and libraries of vectors for use in elucidating mammalian gene function

and identifying and isolating the nucleic acid sequence that inhibit the function of the gene.

Therefore, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to alter the assay in Stark, et al. by using the gene library as the test compounds and to identify and isolate a nucleic acid sequence which inhibits the function of a mammalian gene by infecting a gene library in a cell expressing a selectable marker and isolating the gene which inhibits the function of the mammalian gene as taught in Beach, et al. Thus, the Examiner alleges one would have been motivated to do so because of the expected benefit of identifying genes that encode therapeutically useful compounds as taught by Stark, et al. and elucidating mammalian gene function and identifying inhibitory genes taught by Beach, et al.

The Stark, et al. reference does not teach all the aspects of the present invention. Specifically, it fails to teach isolating a gene/protein that inhibits the transduction of intracellular signals and introducing a cDNA library. Therefore, Applicants respectfully traverse this rejection and request reconsideration.

Stark, et al. teach a method that is completely opposite of the goal of the present invention. Stark, et al. focus on identifying compounds which inhibit the activity of viral proteins, on finding compounds that de-inhibit a cytokine response, and requires the presence of a cytokine-response-inhibitory intracellular amount of a substance that inhibits the response of a cell that responds to the presence of a cytokine. The Stark, et al. method is contrary to the present invention of locating a gene/protein that inhibits the

specific intracellular transduction signals. Further, Stark, et al. teach away from the Applicants' invention. *In re Gurley*, 27 F.3d at 553, 31 U.S.P.Q.2d (BNA) at 1132.

The method taught by Stark, et al. is directed to the identification of compounds that inhibit the activity of viral proteins not the isolation of genes encoding proteins that inhibit the transduction of intracellular signals as is claimed in the present invention. The Stark, et al. system is highly specialized for this singular goal and is not readily adapted for other purposes. Moreover, there is no suggestion of such modifications in the reference.

Under the scheme described in Stark, et al. (shown at the top of page 4), a compound is deemed "useful" if it "inhibits[s] the inhibition by the inhibitory substance (e.g., HBV POL) of the cells response to the stimulating substance (e.g., a substance that causes an increase in cytokine production)" (Stark, et al., p. 3, lines 12-14). Conversely, in the context of the present invention, a gene/protein is deemed "useful" if it inhibits the transduction of specific intracellular signal(s) that operate between specific extracellular stimulation (e.g., cytokine binding) and a promoter region that functions in response to said extracellular stimulation (e.g., the IL-8 promoter). Thus, the two systems have opposite goals; namely Stark, et al. focuses on finding compounds that inhibit the inhibition by an inhibitory substance, whereas, the present invention isolates genes and proteins that inhibit the transduction of specific intracellular signals that operate between a promoter region that responds to extracellular stimulation.

The Stark, et al. system requires the presence of a cytokine-response-inhibitory intracellular amount of a substance (e.g. a viral protein) which inhibits the response of the system (a cell that responds directly or indirectly to the presence of a cytokine or some

other agent to cause cytokine expression or utilization to increase) to the stimulating substance (e.g., a cytokine such as IFN). Thus, in the "control" of the Stark, et al. system, the cytokine response is inhibited or suppressed; it is this "de-inhibition" by the test compound that is the desired result. Conversely, Applicants' system is different: Applicants co-opt a known pathway (e.g., a specific extracellular stimulus leading to specific intracellular activity), transform a host cell accordingly and measure for the interruption of the transduction of one or more intracellular signals. In Applicants' "control", the cytokine response is turned on (rather than suppressed), according to the natural pathway, and it is the inhibition of this natural pathway that is the desired result. Therefore, the present invention provides a method of isolating genes and proteins that inhibit the transduction of one or more intracellular signals, without the need or use of a cytokine-response-inhibitory intracellular amount of a substance. As such, Stark, et al. teaches away from Applicants' invention. *In re Gurley*, 27 F.3d at 553, 31 U.S.P.Q.2d (BNA) at 1132.

The secondary reference cited by the Examiner, Beach, et al., does not cure the deficiency in Stark, et al. The methods disclosed in Beach, et al. are completely different from the techniques of the present invention and lack either an extracellular stimulus, do not identify genes that inhibit specific intracellular signal transduction, or do not determine whether a gene inhibits specific intracellular transduction signals via a promoter and reporter system.

The Beach, et al. reference teaches methods that are completely different from the techniques employed in the present invention and does not teach a method for detecting an inhibitory effect of a test substance on intracellular signal transduction nor a method

for isolating a gene encoding a protein that inhibits specific intracellular signal transduction that operates between a promoter and extracellular stimuli. Beach, et al. disclose three methods of identifying a nucleic acid sequence, namely, a complementation screening method, an antisense method, and a gene trapping method.

The first method of complementation screening is designed to identify a nucleic acid sequence whose expression complements a cellular phenotype. Specifically, infecting a mammalian cell exhibiting the cellular phenotype with a retrovirus particle derived from a cDNA or gDNA-containing retroviral vector of the invention, wherein, upon infection an integrated retroviral provirus is produced and cDNA or gDNA sequence is expressed; and analyzing the cell for the phenotype, so that suppression of the phenotype identifies a nucleic acid sequence which complements the cellular phenotype. (Column 11, line 51-58). This method does not pertain to isolating a gene/protein that inhibits specific intracellular transduction signals that operate between a promoter and extracellular stimuli, but rather deals with inserting DNA into vectors with a gene that does not work to restore the normal function of the gene. The Beach, et al. method is isolating sequences that complement a specific phenotype, which is not the method used in the present invention. Further, the complementation method has no activation in response to a stimulus as in the present invention.

The second method is an antisense genetic suppressor element-based method for the functional inactivation of specific essential and non-essential mammalian genes. Specifically, Beach, et al. teach that identifying a nucleic acid sequence that inhibits the function of a mammalian gene of interest, comprises infecting a mammalian cell with a retrovirus derived from a GSE-producing retroviral vector containing a nucleic acid from

the gene of interest, wherein the cell expresses a fusion protein comprising an N-terminal portion derived from an amino acid sequence encoded by the gene and a C-terminal portion containing a selectable marker, wherein an integrated retroviral provirus is produced that express the cDNA or gDNA sequence; and selecting for the selectable marker and assaying for the marker. (Column 12, line 63 –Column 13, line 9). The reference states that an inhibition of gene function refers to an inhibition of a gene's expression in the presence of a genetic suppressor element (GSE). (Column 12, lines 46-48). Further, the GSE inhibition occurs via an inhibition of translation of transcript produced by the gene of interest. (Column 12, lines 52-54). This method does not pertain to isolating a gene/protein that inhibits specific intracellular transduction signals that operate between a promoter and extracellular stimuli. The reference specifically states, that upon infection an integrated provirus is formed and the nucleic acid sequence is expressed. (Column 13, lines 32-33). This method lacks extracellular stimulation and proceeds to test a gene of interest based upon a cell's own machinery and not stimulation of a promoter. Further, the method is directed at inhibiting mammalian gene function, but does not describe what type of function is inhibited or where the inhibition occurs.

The last method described in Beach, et al. is that of gene trapping. Gene trapping is a method for the identification and isolation of mammalian genes, which are modulated in response to specific stimuli. Specifically, a mammalian cell is infected with a retrovirus derived from a gene trapping vector, wherein upon infection, an integrated provirus is formed. Further, the cell is subjected to a stimulus of interest and assayed for the expression of the reporter sequence so that if the reporter sequence is expressed, it is integrated within, and thereby identifies, a gene that is expressed in the presence of the

stimulus. (Column 15, lines 43-50). This method does not pertain to isolating a gene/protein that inhibits specific intracellular transduction signals that operate between a promoter and extracellular stimuli. The gene trapping method is only identifying genes that respond to a particular stimulus, not isolating a gene that inhibits specific intracellular transduction signals that operates between a promoter and extracellular stimuli. Further, the type of stimulation is not described.

Although, the Beach, et al. reference mentions the use of cDNA in the methods for identifying a nucleic acid sequence, the techniques employed are different from the present invention. The methods either lack an extracellular stimulus, do not identify genes that inhibit specific intracellular signal transduction, or do not determine whether a gene inhibits specific intracellular transduction signals via a promoter and reporter system. Further, the use of cDNA to identify regulatory cytokines as described in the reference, employs a technique not used in the present invention. Specifically, the reference discusses that the growth regulatory cytokines may be identified by expression of cDNA libraries directly in the target cells, but has been hampered in the past by the low transfection efficiencies of the target cell types. (Column 17, lines 39-43). The problem with the approach is that although it will identify trans-acting factors, it also identifies cDNA that also act in cis. (Column 17, lines 50-53). This reference alleges that using a two-cell system can eliminate this problem. (Column 17, lines 53-55). The system described in the reference does not pertain to the present invention, nor does it employ the techniques of the present invention of isolating a gene/protein that inhibits specific intracellular transduction signals that operate between a promoter and extracellular stimuli.

The method of the present invention is a completely different approach to isolating a gene/protein that inhibits specific intracellular transduction signals that operate between a promoter and extracellular stimuli and is not employed in the Stark, et al. and Beach, et al. references. Further, there is no express or implicit motivation to combine the reference because the methods employed by the references are completely different and teach away from the method of the present invention.

Therefore, since Stark, et al. fail to teach the method of the present invention or render it obvious in view of Beach, et al, the present invention is not unpatentable over the cited references.

For at least the foregoing reasons, Applicants respectfully submit that Claims 12, 13 and 20 are patentably distinct from the prior art. Applicants therefore respectfully request withdrawal of the rejection of Claims 12, 13 and 20 under 35 U.S.C. § 103(a).

New Claims

Claims 30-39 have been added. These new claims are believed to introduce no new matter and are supported by the specification, for example, the originally filed claims 2-4, 14-16, and 21-24.

Applicant respectfully submits that claims 12, 13, 20, and 30-39 are in condition for allowance.

Sequence Listing

The Sequence Listing submitted herewith is in response to The Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures attached to the Office Action mailed on October 21,

2002. The Sequence Listing herewith attached complies with the requirements of 37 C.F.R. §§ 1.821-1.825.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant(s) therefore respectfully request(s) that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

SHANKS & HERBERT

By: Tamara Yorita

Tamara Yorita
Reg. No. 53,813

Date: 04-08-03

TransPotomac Plaza
1033 N. Fairfax Street
Suite 306
Alexandria, VA 22314
(703) 683-3600

Marked-up Version of the Claims

1.-11. (Cancelled)

12. (Currently amended) A method for isolating a gene encoding a protein that inhibits transduction of specific intracellular signals ~~transduction~~, wherein the method comprises,

(a) introducing a gene library into ~~the cells of claim 6~~ host cells transformed with a vector holding a gene capable of inducing cell death under specific conditions, wherein said gene is linked downstream of a promoter region that functions in response to a specific extracellular stimulation via said specific intracellular signals;~~;~~

(b) adding the specific extracellular stimulation under the specific conditions to the cells obtained in (a) and screening for living cells ~~screening living cells after the specific extracellular stimulation which causes said specific intracellular signal transduction is added under the specific conditions to the cells that the gene library is introduced into obtained in (a),~~; and

(c) isolating the gene introduced into said cells from the cells screened in (b).

13. (Currently amended) A method for isolating a gene encoding a protein that inhibits transduction of specific intracellular signals ~~transduction~~, wherein the method comprises,

(a) introducing a gene library into ~~the cells of claim~~ 7 hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) deficient host cells transformed with a vector holding a xanthine-guanine-phosphoribosyltransferase gene capable of inducing cell death under specific conditions, wherein said gene is linked

downstream of a promoter region that functions in response to specific extracellular stimulation via said specific intracellular signals;~~,~~

(b) adding the specific extracellular stimulation in the presence of 6-thioguanine to the cells obtained in (a) and screening for living cells ~~after the specific extracellular stimulation which causes specific intracellular signal transduction is added in the presence of 6-thioguanine to the cells that the gene library is introduced into obtained in (a),~~; and

(c) isolating the gene in said cells from the cells screened in (b).

14.-19. (Cancelled)

20. (Currently amended) A method for isolating a gene encoding a protein that inhibits transduction of specific intracellular signals ~~transduction~~, wherein the method comprises,

(a) introducing into host cells a gene library that can be expressed in the host cells and a vector having a reporter gene linked downstream ~~to~~ from a promoter region that functions ~~functioning~~ in response to specific extracellular stimulation via said specific intracellular signals~~,~~;

(b) applying specific extracellular stimulation to the host cells into which the vector in (a) is introduced, detecting the activity of the product of the reporter gene ~~product~~, and selecting cells in which said activity decreases~~,~~; and

(c) isolating a gene introduced into said cells from the cells screened in (b).

21.-29. (Cancelled)

30. (Re-instated – formerly claim # 2) The method of claim 12, wherein said extracellular stimulation is stimulation by cytokine.

31. (Re-instated – formerly claim #3) The method of claim 12, wherein said extracellular stimulation is stimulation by tumor necrosis factor (TNF).

32. (Re-instated – formerly claim #4) The method of claim 31, wherein said promoter region is a promoter region for the interleukin 8 gene.

33. (Re-instated – formerly claim #14) The method of claim 13, wherein said extracellular stimulation is stimulation by cytokine.

34. (Re-instated – formerly claim #15) The method of claim 13, wherein said extracellular stimulation is stimulation by tumor necrosis factor (TNF).

35. (Re-instated – formerly claim #16) The method of claim 34, wherein said promoter region is a promoter region for the interleukin 8 gene.

36. (Re-instated – formerly claim #21) The method of claim 20, wherein said reporter gene is the luciferase gene.

37. (Re-instated – formerly claim #22) The method of claim 20, wherein said extracellular stimulation is stimulation by cytokine.

38. (Re-instated – formerly claim #23) The method of claim 20, wherein said extracellular stimulation is stimulation by tumor necrosis factor (TNF).

39. (Re-instated – formerly claim #24) The method of claim 38, wherein said promoter region is a promoter region for the interleukin 8 gene.